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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/565,591 | 10/06/2006 | David K.R. Karaolis | KARAOLIS1A | 2282 |

1444 7590 11/09/2009

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| EXAMINER | |
|---|---|
| ARCHIE, NINA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 11/09/2009 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/565,591 | KARAOLIS, DAVID K.R. | |
| | Examiner | Art Unit | |
| | Nina A. Archie | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7,9-21 and 28-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *17-21* is/are allowed.

6)☒ Claim(s) *1-7,9-16 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/15/2009 and 7/9/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 15, 2009 and September 15, 2009 has been entered.

### *Amendment Entry*

2. The amendment filed June 15, 2009 and September 15, 2009 has been entered. Claims 1-7, 9-10 have been amended. Claims 1-7, 9-12, 13-21, and 28-30 are pending and under examination.

### *Withdrawal of Rejection*

3. The rejection of claims 17-21 under 35 U.S.C. 112, first paragraph (enablement rejection) has been withdrawn in view of applicant's arguments.

### *Information Disclosure Statement*

4. The information disclosure statement filed on 6/15/09 and 7/9/2009 has been considered. Initialed copies are enclosed.

### *Response to Arguments*

5. Applicant's arguments with respect to claims 1-7, 9-12, 13-16, and 28-30 have been considered but are moot in view of the ground(s) of rejection below.

### *Claim Rejections Maintained*

### *35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejections of claims 1-5, 10-16, and 28-30 under 35 U.S.C. 112, first paragraph failing to comply with the enablement requirement are maintained for the reason set forth in the previous office action. The claim(s) contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Applicant arguments**:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph, September 15, 2009 is carefully considered, but not found to be persuasive for the reasons below.

Applicants argue that the claims are amended without prejudice to refer only to "bacterial" pathogen instead of any "microbial" pathogen. Applicant state the executed 1.132 declaration of David Karaolis attached hereto addresses this rejection as it may relate to "bacterial" pathogens and in light of the evidence and statements from the 1.132 declaration attached hereto and the evidence from the 1.132 declaration submitted with the amendment of October 6, 2008, it is clear that Example 8 on page 80 of the present specification does indeed demonstrate positive results in a challenged mouse model, contrary to the examiner's assertion, and that post-filing in vitro and in vivo experimental results in a broad range of gram positive and gram negative bacterial pathogens confirmed the activity of c-di-GMP and other cyclic dinucleotides in inhibiting microbial colonization, virulence and infection for Staphylococcus aureus in a mouse mastitis model. The applicant's state the bacterial pathogens used in the experiments span from gram-positive cocci, Staphylococcus aureus and Streptococcus pneumoniae (from two different families) to gram negative enteric Klebsiella pneumoniae (from the Enterobacteriaceae family) to gram negative Ehrlichia chaffeensis of the Rickettsiales family to gram negative Brucella melitensis (from the family Brucellaceae). One of skill in the art would certainly appreciate that these representative examples of pathogenic bacteria cover a wide spectrum of bacteria that even includes intracellular bacterial pathogens from the less common bacterial pathogen families of Rickettsiales and Brucellaceae and would therefore

reasonably expect, based on the evidence of record, that the presently claimed method would be enabled for the extended genus of bacterial pathogens.

Applicants argue positive in vitro and in vivo experimental results, as discussed in the attached 1.132 declaration and the 1.132 declaration filed October 6, 2008, were obtained with several different cyclic dinucleotides, including c-di-GMP, TBDMS-c-di-GMP, c-GpAp, c-GpIp and c-GpsGp, thereby providing evidence for the function of cyclic dinucleotides that all share a common core structure of cyclic (head to tail) ribo- or deoxyribo-nucleotides (with ribose moiety and purine or pyrimidine base). One of skill in the art would certainly understand and appreciate from the teachings of the present specification at paragraphs [0044]-[0046] that c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others. Thus, specific cyclic dinucleotides may act as either agonists or antagonists of c-di-GMP, a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification. Applicant also notes that on page 8 of the Advisory Action of May 27, 2009, the examiner cited Bowie et al., Science 247:1306-1310 (1990), for teaching the problem of predicting protein structure from sequence data. This citation is irrelevant as the three dimensional structure of a protein macromolecule has nothing to do with small cyclic dinucleotides, which is more analogous to small organic molecules having a common core structure with only differences in the substituent groups.

**Examiner Response to Applicants Arguments**:

In response to applicant's statement as set forth supra, the 1.132 Declaration by Keith Foster has been fully considered. However, declarant's statement is not deemed persuasive. The Staphylococcus aureus experimental results already presented in the present specification do not provide enablement for a gram positive bacteria. The claims encompass any bacterial pathogen which includes any type of bacteria. Furthermore the instant claims are drawn to reducing the virulence of a bacterial pathogen the claims and are not limited to the reduction in colonization. Therefore the experimental data as disclosed in the declaration are not in commensurate in scope with the claims (see MPEP 716.02) and as such are deem non-persuasive. The limited number of bacterial pathogens and dinculeotides disclosed in the specification and declaration are not

persuasive. The limited number of species disclosed is not deemed to be representative of the genus encompassed by the instant claims. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Eventhough positive in vitro and in vivo experimental results, as discussed in the attached 1.132 declaration and the 1.132 declaration filed October 6, 2008, were obtained with several different cyclic dinucleotides, including c-di-GMP, TBDMS-c-di-GMP, c-GpAp, c-GpIp and c-GpsGp, thereby providing evidence for the function of cyclic dinucleotides that all share a common core structure of cyclic (head to tail) ribo- or deoxyribo-nucleotides (with ribose moiety and purine or pyrimidine base). Examiner disagrees that one of skill in the art the genus of cyclic dinucleotides disclosed in the specification at paragraphs [0044]-[0046] that c-di-GMP may act to inhibit biofilm formation/colonization/virulence in some bacteria or it may act in the opposite manner and induce or enhance biofilm formation/colonization/virulence in others. Applicants states that specific cyclic dinucleotides may act as either agonists or antagonists of c-di-GMP, a property that can be rapidly and readily determined with only routine experimentation using biofilm formation/inhibition assays in microtiter plates, test tubes or flasks, as disclosed in paragraph [0045] and in the examples of the specification. Therefore consequently, declarant's argument that "cyclic dinucleotides" would have been a matter of routine" is not germane.

In regards to the Bowie et al., Science 247:1306-1310 (1990) reference, for teaching the problem of predicting protein structure from sequence data and that said reference is irrelevant as the three dimensional structure of a protein macromolecule has nothing to do with small cyclic dinucleotides, which is more analogous to small organic molecules having a common core structure with only differences in the substituent groups. The claims are drawn to any cyclic dinucleotide therefore using any common structure of a cyclic nucleotide in the methods as claimed is unpredictable based on the teachings of Bowie et al. Therefore one of skill in the art would therefore not reasonably expect, based on the evidence of record, that the presently claimed method would be enabled for the extended genus of bacterial pathogens.

As outlined previously: the specification, while being enabling for a method for attenuating the virulence of a microbial pathogen from *S. aureus or* for inhibiting or reducing

colonization by a microbial pathogen from S. aureus in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP, cGMP and 5'-GMP to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen, does not reasonably provide enablement for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di--GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Nature of the invention. The claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di-GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen.

The breadth of the claims. The method claim is very broad and the product, a cyclic dinucleotides used to administer to a patient is directed to any microbial pathogen. Furthermore the claims are drawn to any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Therefore it is hard for one skilled in the art to determine if any cyclic dinucleotide can be used to attenuate the virulence, inhibit or reduce the colonization or any microbial pathogen in a patient. Since the specification fails to provide particular guidance for any method for attenuating the virulence of a microbial pathogen or for inhibiting or reducing colonization of a microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of any type of a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce

colonization by, the microbial pathogen, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

Guidance in the specification/Working Example. The specification discloses in Example 3 (see pp. 49-67), various examples, such as the effect of c-di-GMP on S. aureus biofilm formation (see 00101), the effects of c-di-GMP on S. aureus pre-formed biofilms (00102), c-di-GMP treatment the prevents cell to cell interaction (see 00111), c-di-GMP inhibiting biofilm formation in human and bovine S. aureus (see 00113), the effects of cGMP and 5'GMP on biofilm formation (see 00116), the effect of c-di-GMP treatment on S. aureus pre-formed biofilms (see 00117), and lastly safety and toxicity tests disclosing the treatment of c-di-GMP on mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic (see 00119-00120). There is no showing in the specification that cyclic dinucleotides can be administered to a patient to attenuate the virulence of a microbial pathogen or for inhibiting or reducing colonization by a microbial pathogen. Although the specification gives several examples of a method for inhibiting microbial colonization and pre-formed microbial biofilm by disclosing various examples, such as in vitro studies of the effects c-di-GMP or any cyclic dinucleotides species there of on pre-formed microbial biofilm or biofilm formation and c-di-GMP treatment that prevents cell to cell interaction (see Example 3), the specification fails to show a method comprising administering to the patient in need an effective amount of c-di-GMP or any cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. Furthermore although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention (see 00119-00120). The specification does not give any working example (i.e. challenged mice models or passive immunization approaches). Therefore the specification fails to describe any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof.

The state of the prior art. The state of the art is unpredictable with regard to administering cyclic dinucleotides to attenuate the virulence of a microbial pathogen or for inhibiting or reducing

colonization in a patient. The state of the art questions the correlation between in vivo and in vitro models for treatment of bacterial/microbial pathogens. For example, Parsek et al proposed four basic criteria to define biofilm-associated infections: (i) Bacterial cell adherence to or association with a surface, (ii) in vivo observation of bacterial cell clusters, (iii) a localized infection pattern, and (iv) increased resistance to antibiotic treatment in the host compared to resistance of genetically equivalent planktonic bacteria. A role for bacterial biofilms in pathogenesis is well established for a number of infections and opportunistic pathogens; for many other infections a link between biofilms and disease has been proposed, but the evidence remains less clear (see Parsek et al 2003. Bacterial biofilms: an emerging link to disease pathogenesis. Annu. Rev. Microbiol. 57:677-701 in its entirety). The state of the art indicate that Reisner et al teach the understanding of *Escherichia coli* biofilm formation in vitro is based on studies of laboratory K-12 strains grown in standard media. The data demonstrate that prevalence and expression of three factors known to strongly promote biofilm formation in *E. coli* K-12 (F-like conjugative pili, aggregative adherence fimbriae, and curli) cannot adequately account for the increased biofilm formation of nondomesticated *E. coli* isolates in vitro. Reisner et al discuss the complexity of genetic and environmental effectors of the biofilm phenotype within the species *E. coli*. Reisner et al teach the results found were a poor correlation between biofilm formation in different media, suggesting that *E. coli* isolates respond very differently to the changing growth and environmental conditions and that this finding emphasizes the relevance and difficulty involved in selecting proper conditions for in vitro biofilm studies which attempt to mirror natural environments in vivo. Reisner et al teach that based the results, in vitro biofilm phenotypes cannot be correlated with the expected virulence phenotypes of the *E. coli* isolates in vivo. Reisner et al further teach that a tremendous impact of environmental conditions highlights the need to develop better biofilm model systems to approximate in vivo situations. Furthermore careful adjustment of the medium composition is an important first step. Incorporation of more adequate surfaces in the experimental design appears to be an additional measure, e.g., by studying biofilm formation directly on eukaryotic cells. However, given that multiple species are present in most environments, we also need to establish models that enable monitoring of possible antagonistic or synergistic interactions between community members (see Reisner et al 2006 Journal of Bacteriology Vol. 188 No. 10 pgs. 3572-3581 see abstract, pg. 3572 column 1

and pg. 3580). Furthermore the art indicates that device related infections are difficult to treat with antibiotics alone and that the minimum inhibitory concentrations (MICs) are not predictive for the therapeutic outcome in either the in vitro or in vivo model. For example the treatment of device related infections between the efficacy of antibiotics and the of drug levels of MICs is poor (see abstract and pg. 1138). Furthermore, the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The state of the art teach that c-di-GMP is a novel naturally occurring nucleotide identified in prokaryotic systems and has found to be active in eukaryotic systems (see Steinberger et al 1999 FEBS LETTERS Vol. 444 pgs. 125-129 specifically pg. 125). Additionally Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Therefore the art questions whether any type of cyclic dinucleotides would have the same effect on the method as claimed.

Furthermore the art has not shown any method of administering any type of cyclic dinucleotides to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. The art questions the correlation between an in vivo and an in vitro model. Therefore, given the lack of success in the art. For the reasons set forth supra, the state of

the art is unpredictable in regards to administering any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient.

In conclusion, the claimed inventions are not enabled for any method for attenuating the virulence of any microbial pathogen or for inhibiting or reducing colonization by any microbial pathogen in a patient in need thereof, comprising administering to the patient in need an effective amount of c-di--GMP or a cyclic dinucleotide to attenuate the virulence of, or to inhibit or reduce colonization by, the microbial pathogen. The state of the art indicates that the clinical relevance of susceptibility testing has always been questioned because of the difficulty of correlating in vitro susceptibility testing with in vivo clinical effectiveness and that there have always been host/pathogen factors that influence the clinical outcome that cannot be predicted by the results of susceptibility testing (see Stratton 2006 Med. Clin North Am Vol. 6 pgs. 1077-1088 see abstract). The art has not shown any method of administering c-di--GMP or any cyclic dinucleotide to attenuate the virulence of any microbial pathogen or for inhibiting or reducing colonization in a patient. Furthermore, the art questions the correlation between an in vivo and an in vitro model. For the reasons set forth supra, the state of the art is unpredictable. There is also a lack of working examples. Although the specification discloses orally administering c-di-GMP to mice that indicates to the inventor that c-di-GMP is relatively safe and not toxic only contemplates the claimed invention. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

***New Grounds of Rejections***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7, 9-21, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a vast genus of cyclic dinucleotides. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. Applicants must adequately describe the genus of cyclic dinucleotides capable of inhibiting or reducing colonization of a bacterial pathogen and attenuating the virulence of a bacterial pathogen.

Applicants have only disclosed the following. The specification disclose c-di-GMP reducing the numbers of *Staphylococcus aureus* (*S. aureus)* adhering to hela cells (see Example 3 and Figure 11B or 00119-00120). Furthermore the specification discloses administering c-di-GMP to mice with an *S. aureus* infection of mastitis and show that treatment shows a significant dose dependent suppressing effect of c-di-GMP on the ability of *S. aureus* to multiply or colonize in the mammary gland (see Example 8 or (00145)). The specification suggests that c-di-GMP can also be used to inhibit biofilm formation of epithelial cell surfaces (see 00119). The specification discloses non-limiting examples of cyclic dinucleotides including c-di-GMP (see 0046).

The data indicated above does not correlate to the claimed functions set forth in the instant claims and do not provide adequate description of the claimed invention. Applicant has not demonstrated that any cyclic dinucleotide can possess the abilities of inhibiting or reducing colonization of any bacterial pathogen and attenuating the virulence of any bacterial pathogen as claimed. Furthermore, the limited number of species (for ex. c-di-GMP reducing the numbers of *Staphylococcus aureus* (*S. aureus)* adhering to hela cells) aforementioned above and disclosed in

the specification is not deemed to be representative of the genus of cyclic of dinuclucleotides encompassed by the instant claims. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Therefore, although the specification discloses examples of cyclic dinucleotides, the specification does not teach any structural limitations and the specification is silent to the correlation of the genus of cyclic dinucleotides and its recited function.

Moreover, the specification, does not disclose distinguishing and identifying features of a representative member of the genus of cyclic dinucleotides to which the claims are drawn, such as a correlation between structure of the cyclic dinucleotides and its recited functions capable of inhibiting or reducing colonization a bacterial pathogen and attenuating the virulence of a bacterial pathogen, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of cyclic dinucleotides. Moreover, Applicant has not demonstrated that any cyclic dinucleotides aforementioned above is capable of inhibiting or reducing colonization a bacterial pathogen and attenuating the virulence of a bacterial pathogen. Moreover, there is no empirical data reported in the specification at the time of filing showing efficacy of inhibiting a bacterial pathogen and attenuating the virulence of a bacterial pathogen of the function as claimed in the method. Moreover, the specification is silent with regard to what core structure needs to be present for the cyclic dinucleotide to function as directed in the claim.

Therefore, the specification lacks written description of the instant claimed invention. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus aforementioned above.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Ink's. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991 ). Furthermore, the written

description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Therefore, absent a detailed and particular description of a representative number of the members of the genus of cyclic dinucleotides, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of cyclic dinucleotides with the recited activities. Therefore, in accordance with the *Guidelines*, the description of cyclic dinucleotides or c-di-GMP is not deemed representative of the genus of cyclic dinucleotides to which the claims refer and therefore the claimed invention is not properly disclosed.

***Citation of Relevant Art***

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ross et al. Biol. Chem. 265 No. 31 (1990) 18933-18943 teaches the effects of c-di-GMP and other cyclic dinucleotides on cellulose synthetase.

***Conclusion***

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/

for Nina Archie, Examiner of Art Unit 1645